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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/616,849 | BURCHARD, JULJA | |
| | Examiner | Art Unit | |
| | BJ Forman | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *27-30,33-40,42-54,59-68,73-75,84,85 and 90-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-30,33-40,42-54,59-68,73-75,84,85 and 90-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

**FINAL ACTION**

1. This action is in response to papers filed 26 December 2002 in which claims 27, 48-54, 67, 75 and 90 were amended, claims 57-58 and 71-72 were canceled and claims 91-104 were added. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action dated 25 September 2002 are withdrawn in view of the amendments. All of the arguments have been thoroughly reviewed but are deemed moot in view of the amendments, withdrawn rejections and new grounds for rejection. However, the arguments are discussed below as they apply to the new rejections.

New grounds for rejection are discussed.

Claims 27-30, 33-40, 42-54, 59-68, 73-75, 84-85 and 90-104 are under prosecution.

***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 27-30, 33-36, 44-47, 59-68, 73-75, 90, 91 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al (U.S. Patent No. 6,344,316 B1, filed 25 June 1997) in view of Bao et al (U.S. Patent No. 251,601, filed 2 February 1999).

Regarding Claim 27, Lockhart et al teach a method for evaluating a binding property of a polynucleotide probe comprising a predetermined nucleotide sequence to a target nucleotide sequence, said method comprising: comparing the amount of hybridization of polynucleotide in a first sample to the probe with the amount of hybridization of polynucleotides in a second sample to the probe wherein the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and said second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide comprises a sequences that is different from the sequences of other polynucleotides and wherein at least 75% of the polynucleotides in the first sample are polynucleotides comprising said target sequence thereby evaluating said binding property of said probe (Column 36, lines 24-47 and Example 1, Column 70, line 58-Column 73, line 46). Lockhart et al further teach that the amount of hybridization signal from the first and second sample are compared to evaluate binding properties of the probe (Column 36, lines 24-47). While they do not specifically teach the comparison comprises determining a ratio, their method clearly suggests that the comparison encompasses determining a ration because they select probe based on the measured comparison and select probes preferably having a signal greater than 50% background (i.e. second sample) (Column 37, lines 42). Additionally, signal intensity and hybridization ratios were well known in the art at the time the claimed invention was made as taught by Bao et al who teach that the ratio of signal to background is the most important information for quality control (Column 16, line 45-Column 17, line 62, especially Column 17, lines 25-36). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the ratio determination taught by Bao et al and to determine the ratio of the hybridization amounts of the first sample to the second sample. One of ordinary skill in the

art would have been motivated to determine the ratio based on the teaching of Bao et al wherein the ratio between signal and background is the most important information for quality control (Column 17, lines 25-36).

Regarding Claim 28, Lockhart et al teach the method wherein the predetermined sequence of the probe is complementary to at least a hybridizable portion of the target sequence in the first sample (Column 36, lines 33-39).

Regarding Claim 29, Lockhart et al teach the method wherein the target polynucleotide sequence in the first sequence is a sequence of a gene or gene transcript or of an mRNA, cDNA derived therefrom (Column 36, lines 24-47).

Regarding Claim 30, Lockhart et al teach the method wherein the different polynucleotides in the second sample comprise sequences of a plurality of gene transcripts of a cell or organism (Column 36, lines 24-47).

Regarding Claims 33-35, Lockhart et al teach the method wherein at least 90% (Claim 33); at least 95% (Claim 34); and at least 99% (Claim 35) of the polynucleotides in said first sample are polynucleotides comprising said target sequence i.e. "target nucleic acid alone" (Column 36, lines 33-35).

Regarding Claim 36, Lockhart et al teach the method wherein each different polynucleotide in the second sample does not comprise the target sequence (Column 36, lines 33-37).

Regarding Claims 44-47, Lockhart et al teach the method wherein the amount of polynucleotides in the first sample comprising the target sequence differs from the amount of polynucleotides in the second sample comprising the target sequence by at least a factor of four (Claim 44); by at least a factor of eight (Claim 45); by at least a factor of 20 (Claim 46); and by at least a factor of 100 (Claim 47) i.e. the second sample does not comprise the target sequence (Column 36, lines 33-37).

Regarding Claim 59, Lockhart et al teach the method wherein the polynucleotides in the first sample are detectably labeled (Column 24, lines 7-67).

Regarding Claim 60, Lockhart et al teach the method wherein the polynucleotides in the second sample are detectably labeled (Column 24, lines 7-67).

Regarding Claim 61, Lockhart et al teach the method wherein the polynucleotides are labeled with a fluorescent molecule (Column 24, lines 54-67).

Regarding Claim 62, Lockhart et al teach the method wherein the polynucleotides in the first sample are labeled with a first label and the polynucleotides in the second sample are labeled with a second label the first label being distinguishable from the second (Column 24, lines 54-67).

Regarding Claim 63, Lockhart et al teach the method wherein the first and second labels are fluorescent molecules (Column 24, lines 54-67).

Regarding Claim 64, Lockhart et al teach the method wherein the probe is attached to a surface of a support (Column 36, lines 24-30).

Regarding Claim 65, Lockhart et al teach the probe is one of a plurality of probes (Column 36, lines 24-30).

Regarding Claim 66, Lockhart et al teach the method wherein the plurality of probes comprises polynucleotide probes in an array of probes said array having a support with at least one surface and different probes attached to said surface wherein each of said different probes attached is attached in a different location (Column 34, lines 24-30).

Regarding Claim 67, Lockhart et al teach a method for evaluating a binding property of a plurality of polynucleotide probes to a target sequence wherein each probe comprises a predetermined nucleotide sequence, said method comprising comparing the amount of hybridization of polynucleotide in a first sample to each probe with the amount of hybridization of polynucleotides in a second sample to each probe wherein the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and said

second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide comprises a sequences that is different from the sequences of other polynucleotides and wherein at least 75% of the polynucleotides in the first sample are polynucleotides comprising said target sequence thereby evaluating said binding property of said probe (Column 36, line 24-47). Lockhart et al further teach that the amount of hybridization signal from the first and second sample are compared to evaluate binding properties of the probe (Column 36, lines 24-47). While they do not specifically teach the comparison comprises determining a ratio, their method clearly suggests that the comparison encompasses determining a ration because they select probe based on the measured comparison and select probes preferably having a signal greater than 50% background (i.e. second sample) (Column 37, lines 42). Additionally, signal intensity and hybridization ratios were well known in the art at the time the claimed invention was made as taught by Bao et al who teach that the ratio of signal to background is the most important information for quality control (Column 16, line 45-Column 17, line 62, especially Column 17, lines 25-36). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the ratio determination taught by Bao et al and to determine the ratio of the hybridization amounts of the first sample to the second sample. One of ordinary skill in the art would have been motivated to determine the ratio based on the teaching of Bao et al wherein the ratio between signal and background is the most important information for quality control (Column 17, lines 25-36).

Regarding Claim 68, Lockhart et al teach the method wherein the predetermined sequence of each probe is complementary to at least a hybridizable portion of the target sequence in the first sample (Column 36, lines 33-39).

Regarding Claim 73, Lockhart et al teach the method wherein each probe is attached to a surface of a support (Column 36, lines 24-30).

Regarding Claim 74, Lockhart et al teach the method wherein the plurality of probes comprises polynucleotide probes in an array of probes said array having a support with at least one surface and different probes attached to said surface wherein each of said different probes attached is attached in a different location (Column 34, lines 24-30).

Regarding Claim 75, Lockhart et al teach the method wherein the first sample comprises two or more different polynucleotide molecules (i.e. "probes of the high density array are then hybridized with their target") wherein none of the plurality of different polynucleotide molecules hybridizes or cross-hybridizes to a probe that also hybridizes or cross-hybridizes to another of the plurality of different polynucleotide molecules (Column 36, lines 24-47).

Regarding Claim 90. Lockhart et al teach the method wherein the polynucleotide molecules comprising the target sequence are the same (Column 36, lines 33-34).

Regarding Claim 91, Lockhart et al teach a method for evaluating a binding property of a plurality of polynucleotide probes to a target sequence wherein each probe comprises a predetermined nucleotide sequence, said method comprising comparing the amount of hybridization of polynucleotide in a first sample to each probe with the amount of hybridization of polynucleotides in a second sample to each probe wherein the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and said second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide comprises a sequences that is different from the sequences of other polynucleotides and not comprising the target sequence and wherein at least 75% of the polynucleotides in the first sample are polynucleotides comprising said target sequence thereby evaluating said binding property of said probe (Column 36, line 24-47). Lockhart et al further teach that the amount of hybridization signal from the first and second sample are compared to evaluate binding properties of the probe (Column 36, lines 24-47). While they do not specifically teach the comparison comprises determining a ratio, their method clearly suggests that the comparison encompasses determining a ration because they select probe based on the

measured comparison and select probes preferably having a signal greater than 50% background (i.e. second sample) (Column 37, lines 42). Additionally, signal intensity and hybridization ratios were well known in the art at the time the claimed invention was made as taught by Bao et al who teach that the ratio of signal to background is the most important information for quality control (Column 16, line 45-Column 17, line 62, especially Column 17, lines 25-36). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the ratio determination taught by Bao et al and to determine the ratio of the hybridization amounts of the first sample to the second sample. One of ordinary skill in the art would have been motivated to determine the ratio based on the teaching of Bao et al wherein the ratio between signal and background is the most important information for quality control (Column 17, lines 25-36).

Regarding Claim 93, Lockhart et al teach a method for evaluating a binding property of a plurality of polynucleotide probes to a target sequence wherein each probe comprises a predetermined nucleotide sequence, said method comprising comparing the amount of hybridization of polynucleotide in a first sample to each probe with the amount of hybridization of polynucleotides in a second sample to each probe wherein the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and said second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide comprises a sequences that is different from the sequences of other polynucleotides and wherein at least 75% of the polynucleotides in the first sample are polynucleotides comprising said target sequence thereby evaluating said binding property of said probe (Column 36, line 24-47). Lockhart et al further teach that the amount of hybridization signal from the first and second sample are compared to evaluate binding properties of the probe (Column 36, lines 24-47). While they do not specifically teach the comparison comprises determining a ratio, their method clearly suggests that the comparison encompasses determining a ration because they select probe based on the measured

comparison and select probes preferably having a signal greater than 50% background (i.e. second sample) (Column 37, lines 42). Additionally, signal intensity and hybridization ratios were well known in the art at the time the claimed invention was made as taught by Bao et al who teach that the ratio of signal to background is the most important information for quality control (Column 16, line 45-Column 17, line 62, especially Column 17, lines 25-36). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the ratio determination taught by Bao et al and to determine the ratio of the hybridization amounts of the first sample to the second sample. One of ordinary skill in the art would have been motivated to determine the ratio based on the teaching of Bao et al wherein the ratio between signal and background is the most important information for quality control (Column 17, lines 25-36).

4. Claims 37-40, 42, 43, 48-54, 84, 85, 90, 92 and 94-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lockhart et al (U.S. Patent No. 6,344,316 B1, filed 25 June 1997) in view of Bao et al (U.S. Patent No. 251,601, filed 2 February 1999) as applied to Claims 27, 67, 91 and 93 above and further in view of Brown et al (U.S. Patent No. 5,807,522, issued 15 September 1998).

Regarding Claim 37, Lockhart et al teach a method for evaluating a binding property of a polynucleotide probe comprising a predetermined nucleotide sequence to a target nucleotide sequence, said method comprising: comparing the amount of hybridization of polynucleotide in a first sample to the probe with the amount of hybridization of polynucleotides in a second sample to the probe wherein the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and said second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide comprises a sequences

that is different from the sequences of other polynucleotides and wherein at least 75% of the polynucleotides in the first sample are polynucleotides comprising said target sequence thereby evaluating said binding property of said probe wherein each different polynucleotide in the second sample does not comprise the target sequence wherein the target sequence is a gene sequence and wherein the probes comprise perfect match and mismatch probes (Column 36, lines 24-47 and Example 1, Column 70, line 58-Column 73, line 46) but they do not specifically teach the second sample comprises a sample from a deletion mutation. Brown et al. teach a similar method for evaluating binding of a plurality of polynucleotide probes to a target polynucleotide wherein each probe has a particular nucleotide sequence, said method comprising comparing the amount of hybridization in a first sample to the amount of hybridization in a second sample and wherein the first sample comprises a plurality of the same target polynucleotides (i.e. amplified copies of fragments from the large chromosomes) and the second sample comprises a plurality of different polynucleotide molecules wherein the different polynucleotide molecules have a different nucleotide sequence (i.e. the second sample comprises amplified copies of fragments from the small chromosomes) (Example 1, Column 16, line 39-56) wherein the target polynucleotide in the first sample corresponds to a gene or gene transcript i.e. the target is from a chromosome which contains genes and therefore the target "corresponds" to a gene (Column 16, lines 39-45) and they teach an embodiment of their method wherein the second sample comprises a sample from a deletion mutant wherein the deletion mutant does not express the gene (Column 15, lines 5-18). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the polynucleotides in the second sample of Lockhart et al with the deletion mutation of Brown et al. to thereby analyze and evaluate mutation-specific probes for the obvious benefits of providing accurate means of mutation detection and diagnosis.

Regarding Claim 38, Brown et al. teach the method wherein the polynucleotides in the second sample comprises polynucleotides having the same sequence as polynucleotides in the

first sample and a plurality of different polynucleotides i.e. the different polynucleotides produce a green signal and the polynucleotides having the same sequence produce an orange signal (Column 17, lines 9-17). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the polynucleotides in the second sample of Lockhart et al by including the target sequence along with the plurality of different sequences as taught by Brown et al. to thereby analyze and evaluate cross-hybridization of the probes for the obvious benefits of providing accurate means of mutation detection and diagnosis.

Regarding Claim 39, Lockhart et al teach the method wherein the target sequence comprises the sequence of a gene transcript and the second sample comprises a sample from a wild-type strain (Column 36,lines 24-47)

Regarding Claim 40, Lockhart et al teach the method wherein the first sample comprises target sequence and the second sample lack polynucleotides comprising the target sequence (Column 36, lines 24-47) but they do not teach the first sample comprises molecules that do not comprise the target sequence. Brown et al. teach the similar method wherein the first sample comprises polynucleotide molecules having a sequence different from the target polynucleotide (i.e. the sample has more than one different polynucleotides of different sequence) and the second sample lacks the different polynucleotides i.e. the red fluorescent signal identifies polynucleotides in the first sample lacking in the second sample (Column 17, lines 9-17). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the first sample of Lockhart et al by adding molecules not comprising the target sequence as taught by Brown et al and to analyze cross-hybridization between target-specific probes to thereby select non-cross-hybridizing probes for the obvious benefits of providing means for accurate sequence hybridization and analysis.

Regarding Claim 42, Lockhart et al teach the method wherein the target sequence is a gene transcript and the first sample comprises a sample from a wild-type cell which expressed the gene transcripts (Column 36, lines 24-47) but they do not teach the second sample

comprising a sample from a deletion which does not express the gene transcript. Brown et al. teach the similar method wherein the second sample comprises a sample from a deletion mutant wherein the deletion mutant does not express the gene (Column 15, lines 5-18). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the polynucleotides in the second sample of Lockhart et al with the deletion mutation of Brown et al. to thereby analyze and evaluate mutation-specific probes for the obvious benefits of providing accurate means of mutation detection and diagnosis.

Regarding Claim 43, Lockhart et al teach the method wherein the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and said second sample comprises a plurality of different polynucleotide molecules wherein the amount of polynucleotides in the first sample comprising the target sequence differs from the amount of polynucleotides in the second sample comprising the target sequence by at least a factor of four i.e. the second sample does not comprise the target sequence (Column 36, lines 24-47) but they do not teach the first sample comprises molecules that do not contain the target sequence and the second sample comprises the molecules comprising the target sequence. Brown et al. teach the similar method wherein the first sample comprises polynucleotide molecules having a sequence different from the target polynucleotide (i.e. the sample has more than one different polynucleotide of different sequence) and the second sample comprises polynucleotides having the same sequence as the target and a plurality of different polynucleotides i.e. the green fluorescent signal identifies polynucleotides in the first sample lacking in the second sample, the red fluorescent signal identifies polynucleotides different from the first sample and yellow fluorescent signal identifies polynucleotides common between the samples (Column 18, lines 5-17). ). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the first sample of Lockhart et al by adding molecules not comprising the target sequence as taught by Brown et al and to analyze cross-hybridization between target-specific probes to thereby select non-

cross-hybridizing probes for the obvious benefits of providing means for accurate sequence hybridization and analysis.

Regarding Claim 48-54, Lockhart et al teach the method wherein the first sample does not contain polynucleotides comprising the target sequence (Column 36, lines 24-47) However, Brown et al. teach the similar method wherein the amount of the polynucleotides in the first and second sample differ by no more than a factor of 100 (Claim 48); differ by no more than a factor of 10 (Claim 49); differ by no more than 50% (Claim 50); differ by no more than a factor of two (Claim 51); and the abundances differ no more than 50% (Claim 52); by nor more than 10% (Claim 53); and differ by no more than 1% (Claim 54); i.e. the amount and abundance are the same (Column 17, lines 65-67). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the equal amount and abundance of polynucleotides as taught by Brown et al to the probe analysis samples of Lockhart et al to thereby control sample quantities based on experimental design and thereby evaluate probe binding under controlled conditions for the obvious benefits of accurately evaluating probe binding during desired experimental conditions.

Regarding Claim 84, Lockhart et al teach the method wherein the polynucleotides in the first sample are labeled with a first label and the polynucleotides in the second sample are labeled with a second label the first label being distinguishable from the second (Column 24, lines 54-67) but they do not teach the step of comparing comprises concurrently contacting the probe with the first and second sample. However, Brown et al. teach the similar method wherein polynucleotides in the first sample are labeled with a first label and polynucleotides in the second sample are labeled with a second label distinguishable from the first label and further comprising concurrently contacting the probe with the first and second sample under conditions conductive to hybridization and detecting binding that occurs between the probe and polynucleotides in the first and second sample (Column 16, line 57-Column 17, line 8). It would have been obvious to one of ordinary skill in the art at the time the claimed invention

was made to modify the sequential hybridization of Lockhart et al with the concurrent hybridization of Brown et al and to hybridize the first and second samples to the probes concurrently thereby eliminating Lockhart's second hybridization step for the obvious benefits of simplification and economy of time.

Regarding Claim 85, Lockhart et al teach the method wherein the second sample lacks polynucleotides of the first sample (Column 36, lines 24-47).

Regarding Claim 90. Lockhart et al teach the method wherein the polynucleotide molecules comprising the target sequence are the same (Column 36, lines 33-34).

Regarding Claim 92, Lockhart et al teach the method wherein the target sequence is a gene transcript and the first sample comprises a sample from a wild-type cell which expressed the gene transcripts (Column 36, lines 24-47) but they do not teach the second sample comprising a sample from a deletion which does not express the gene transcript. Brown et al. teach the similar method wherein the second sample comprises a sample from a deletion mutant wherein the deletion mutant does not express the gene (Column 15, lines 5-18). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the polynucleotides in the second sample of Lockhart et al with the deletion mutation of Brown et al. to thereby analyze and evaluate mutation-specific probes for the obvious benefits of providing accurate means of mutation detection and diagnosis.

Regarding Claim 94, Lockhart et al teach the method wherein the target sequence is a gene transcript and the first sample comprises a sample from a wild-type cell which expressed the gene transcripts (Column 36, lines 24-47) but they do not teach the second sample comprising a sample from a deletion which does not express the gene transcript. Brown et al. teach the similar method wherein the second sample comprises a sample from a deletion mutant wherein the deletion mutant does not express the gene (Column 15, lines 5-18). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the polynucleotides in the second sample of Lockhart et al with the

deletion mutation of Brown et al. to thereby analyze and evaluate mutation-specific probes for the obvious benefits of providing accurate means of mutation detection and diagnosis.

Regarding Claim 95, Lockhart et al teach the method wherein the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and said second sample comprises a plurality of different polynucleotide molecules wherein the amount of polynucleotides in the first sample comprising the target sequence differs from the amount of polynucleotides in the second sample comprising the target sequence by at least a factor of four i.e. the second sample does not comprise the target sequence (Column 36, lines 24-47) but they do not teach the first sample comprises molecules that do not contain the target sequence and the second sample comprises the molecules comprising the target sequence. Brown et al. teach the similar method wherein the first sample comprises polynucleotide molecules having a sequence different from the target polynucleotide (i.e. the sample has more than one different polynucleotide of different sequence) and the second sample comprises polynucleotides having the same sequence as the target and a plurality of different polynucleotides i.e. the green fluorescent signal identifies polynucleotides in the first sample lacking in the second sample, the red fluorescent signal identifies polynucleotides different from the first sample and yellow fluorescent signal identifies polynucleotides common between the samples (Column 18, lines 5-17). ). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the first sample of Lockhart et al by adding molecules not comprising the target sequence as taught by Brown et al and to analyze cross-hybridization between target-specific probes to thereby select non-cross-hybridizing probes for the obvious benefits of providing means for accurate sequence hybridization and analysis.

Regarding Claims 96-99, Lockhart et al teach the method wherein the amount of polynucleotides in the first sample comprising the target sequence differs from the amount of polynucleotides in the second sample comprising the target sequence by at least a factor of four

(Claim 44); by at least a factor of eight (Claim 45); by at least a factor of 20 (Claim 46); and by at least a factor of 100 (Claim 47) i.e. the second sample does not comprise the target sequence (Column 36, lines 33-37).

Regarding Claim 100-104, Lockhart et al teach the method wherein the first sample does not contain polynucleotides comprising the target sequence (Column 36, lines 24-47) Brown et al. teach the similar method wherein the amount of the polynucleotides in the first and second sample differ by no more than 50% (Claim 100); differ by no more than a factor of two (Claim 101); and the abundances differ no more than 50% (Claim 102); by nor more than 10% (Claim 103); and differ by no more than 1% (Claim 104); i.e. the amount and abundance are the same (Column 17, lines 65-67). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the equal amount and abundance of polynucleotides as taught by Brown et al to the probe analysis samples of Lockhart et al to thereby control sample quantities based on experimental design and thereby evaluate probe binding under controlled conditions for the obvious benefits of accurately evaluating probe binding during desired experimental conditions.

**Response to Arguments**

5. Applicant argues that while Lockhart et al teach comparing hybridization abilities to target and non-target samples, Lockhart et al do not teach that a ratio of hybridizations can be used as a measure of binding property of a probe. Applicant further argues that Brown et al do not supply what is missing in Lockhart. The arguments have been considered but are deemed moot in view of the fact that the argument addresses the newly added limitations and new grounds for rejection necessitated by the amendments as discussed above.

Regarding the combination of Lockhart and Brown, Applicant argues that Lockhart's sequential hybridization and hybridization comparison as modified by Brown would not teach the instant invention because Lockhart et al does not teach determining a ratio. The argument has been considered but is deemed moot in view of the amendments and new grounds for rejection incorporating the teaching of Bao et al as discussed above. Specifically, while Lockhart do not explicitly teach determining a ratio for the compared hybridization signals, they clearly suggest determining a ratio because they teach probe selection based on a measured and compared hybridization signals and select probes preferably having a signal greater than 50% background wherein the background signal is derived from the second sample) (Column 37, lines 42). Furthermore, signal intensity and hybridization ratios were well known in the art at the time the claimed invention was made as taught by Bao et al who teach that the ratio of signal to background is the most important information for quality control (Column 16, line 45-Column 17, line 62, especially Column 17, lines 25-36). One of ordinary skill in the art would have been motivated to combine the teachings of Lockhart and Bao and to determine the ratio of first and second (i.e. background) hybridization signals based on the teaching of Bao et al wherein the ratio between signal and background is the most important information for quality control (Column 17, lines 25-36).

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

**Conclusion**

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
April 3, 2003